ORGANIC LETTERS

2009
Vol. 11, No. 24
5662−5664

Dramatic Effect of Solvent Hydrogen Bond Basicity on the Regiochemistry of S_NAr Reactions of Electron-Deficient Polyfluoroarenes

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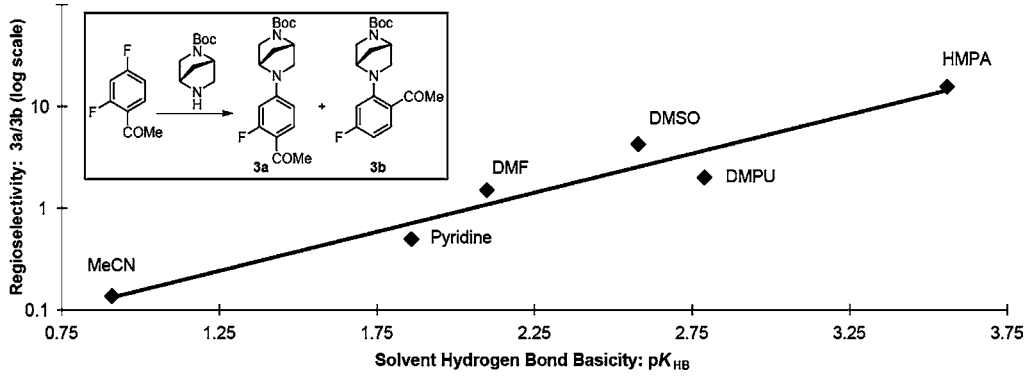
Received October 12, 2009

ABSTRACT



It was found that solvent hydrogen bond basicity (SHBB) significantly affects the regiochemistry of the S_NAr reaction between secondary amines and activated polyfluoroarenes. A plausible mechanism involving a six-membered transition state is invoked for the formation of an *ortho*-substituted isomer, which is likely organized by a hydrogen bond. Evidence for this hypothesis is presented, and a regioselective amination reaction of activated polyfluoroarenes has been developed.

Hydrogen bonding interactions can play a determining role in organic synthesis, as exemplified by the recent development of chiral hydrogen bond donors in asymmetric organocatalysis.[1] Additionally, solvents have long been recognized as one of the most common variables for reaction optimization.[2] While discussions about solvent effects are frequently included in synthetically oriented publications, to the best of our knowledge, the concept of solvent hydrogen bond basicity (SHBB), well-known in the field of physical organic chemistry,[3] has not been reported in a synthetic application. In this communication, we report a dramatic effect of SHBB on the regiochemistry of S_NAr reactions involving electron-deficient polyfluoroarenes, leading to the discovery of a regioselective synthesis of aminofluoroarenes.

In a program to prepare inhibitors of B-Raf kinase as cancer therapeutics,[4] it was found that the S_NAr reaction[5] (eq 1), under typical conditions,[6] of 2,4-difluoroacetophenone (**1**) with (1*S*,4*S*)-*tert*-butyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**2**) gave a mixture of regioisomers only slightly favoring the desired

(1) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.
(2) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 2003; pp 147−328 and 472−475.

(3) (a) Laurence, C.; Berthelot, M. *Perspect. Drug Discovery Des.* **2000**, *18*, 39–60. (b) Taft, R. W.; Gurka, D.; Joris, L.; Schleyer, P. R.; Rakshys, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 4801–4808. (c) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073–4086. (d) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377. (e) Besseau, F.; Laurence, C.; Berthelot, M. *Bull. Soc. Chim. Fr.* **1996**, *133*, 381–387. (f) Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091–2094.

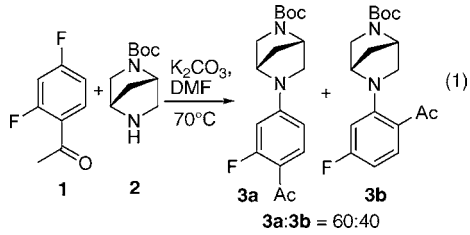
10.1021/ol902353t
Published on Web 11/13/2009

Table 1. Solvent Effect on the Regioselectivity of Reaction [1,a]

solvent	**3a**:**3b**[b]	ε_r[c]	pK_{HB}[d]
toluene	<2:98	2.38	−0.36[3e]
dioxane	<2:98	2.21	1.03[3a]
MeCN	12:88	35.94	0.91[3a]
pyridine	33:67	12.91	1.86[3a]
DMF	60:40	36.71	2.10[3f]
DMPU[e]	67:33	36.12	2.79[3f]
DMSO	81:19	46.45	2.58[3a]
HMPA	*94:6*	*28.30*	*3.56*[3a]

[a] Reaction conditions: 0.05 mmol of **2**, 1.2 equiv of **1**, 3.0 equiv of K_2CO_3, 1 mL of solvent, 70 °C, 24 h. [b] Determinated by ^{1}H NMR. [c] Relative dielectric constant.[2] [d] A scale for hydrogen bond basicity.[3] [e] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

para-isomer **3a** despite the steric hindrance for the *ortho*-isomer **3b**. As the separation of these isomers was nontrivial on the targeted scale, we began a systematic effort to optimize the regioselectivity of this reaction.



Screening[7] of alternative bases and the addition of catalysts such as DMAP did not yield any improvement in selectivity; however, a breakthrough came during an extensive solvent survey (Table 1). It was found that hexamethylphosphoramide (HMPA) is superior to other solvents, providing a 94:6 mixture of **3a** and **3b**. Although the *para* product appeared to be preferred in more polar solvents, acetonitrile gave mainly the *ortho* product. A careful analysis of the relationship between the *ortho*/*para* isomer ratios and SHBB revealed that solvents with high hydrogen basicity tend to give more *para*-substituted product (Figure 1). The pK_{HB} parameter, which was first introduced by Taft,[3b] can be used as a measurement of SHBB. From acetonitrile to HMPA, the regioselectivity jumps from 12:88 to 94:6 in line with the pK_{HB} increase from 0.91 to 3.56. Other polar solvents examined, having pK_{HB} between these two, gave intermediate regioselectivities. The dielectric constants of all these solvents are relatively similar.

We continued our investigation by considering possible mechanisms[8] for the formation of the regioisomers (Scheme 1). The concept of "built-in solvation," first proposed by Bunnett,[9] describes the favorable interaction between the

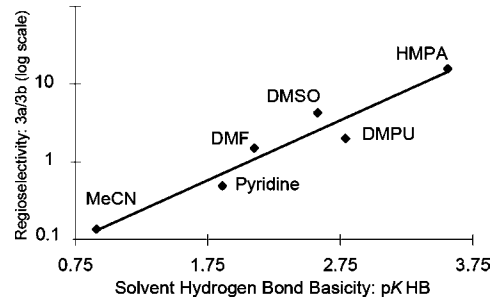
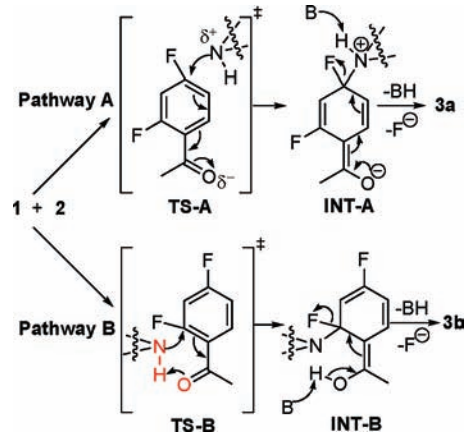


Figure 1. Relationship of the regioselectivity of reaction 1 to solvent hydrogen bond basicity.

Scheme 1. Plausible Mechanism for the Formation of Regioisomers in the S_NAr Reaction [1]



nucleophile amine and nitro group in the transition state of the S_NAr reaction of *ortho*-chloronitrobenzene through either hydrogen bonding[10] or electrostatic attraction. In our system, built-in solvation may also play an important role in the formation of the *ortho*-isomer. In Pathway A, amine **2** attacks the *para* position to yield a zwitterionic intermediate **INT-A** via a partially charged transition state **TS-A**, consistent with the observation that solvents with high dielectric constants give more of the *para*-isomer. In Pathway B, leading to *ortho* isomer **3b**, a neutral intermediate **INT-B** is formed via a cyclic transition state **TS-B**, which is stabilized by an intramolecular hydrogen bond between the amine hydrogen and the carbonyl oxygen, as an example of Bunnett's built-in solvation effect. In the case of *para* substitution, the stabilization of **TS-A** heavily relies on solvation. Therefore, solvents with high SHBB can accelerate Pathway A by hydrogen bonding strongly with the amine protons[11] while having little effect on Pathway B.

(4) Levin, J. I.; Hopper, D. W.; Torres, N.; Dutia, M. D.; Berger, D. M.; Wang, X.; Di Grandi, M. J.; Zhang, C.; Dunnick, A. L. Bridged, Bicyclic Heterocyclic Or Spiro Bicyclic Heterocyclic Derivatives Of Pyrazolo[1, 5-A]Pyrimidines, Methods For Preparation And Uses Thereof. WO 2009/108838, September 3, 2009.

(5) For a recent review of SNAr reactions, see: Crampton, M. R. Nucleophilic Aromatic Substitution. In *Organic Reaction Mechanisms, 2005*; Knipe, C., Eds.; John Wiley & Sons: West Sussex, UK, 2008; pp 155−165.

(6) Lee, K. H.; McPhee, F.; DeVoss, J. J.; Craik, C. S.; Ortiz de Montellano, P. R. *J. Org. Chem.* **1994**, *59*, 6194–6199.

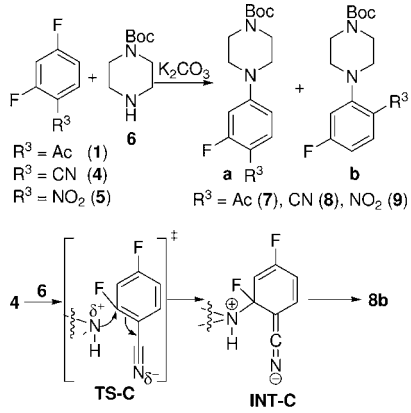
(7) Details in Supporting Information(Table S1, Table S2).

(8) For a mechanism discussion of the classical S_NAr reaction, see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanism 4th*; Kluwer Academic/Plenum Publishers: New York, Boston, Dordrecht, London, Moscow, 2004; pp 589−593.

(9) Bunnett, J. F.; Morath, R. J. *J. Am. Chem. Soc.* **1955**, *77*, 5051–5055.

(10) Bishop, R. R.; Cavell, E. A. S.; Chapman, N. R. *J. Chem. Soc.* **1952**, 437–446.

Scheme 2. Solvent Effect on the Regioselectivity of the S_NAr Reactions of Amine **6** and Difluoroarenes Containing Acyl, Nitro, or Cyano as Activating Groups[a]



sub.	prod.	dioxane	MeCN	HMPA	**IL1**[b]	**IL2**[c]
1	**7a:7b**	<2:98[d]	8:92	91:9	96:4	15:85
4	**8a:8b**	50:50	88:12	93:7	87:13	91:9
5[e]	**9a:9b**	<2:98	5:95	67:33	89:11[f]	11:89

[a] Reaction conditions: 1.0 equiv **6**, 1.2 equiv **1**/**4**/**5**, 3.0 equiv K_2CO_3, 70 °C, 60 h. [b] 1-Ethyl-3-methylimidazolium dimethyl phosphate. [c] 1-Butyl-3-methylimidazolium hexafluorophosphate. [d] 100 °C, 48 h. [e] rt, 120 h. [f] A 1:1 mixture of DMF and **IL1** was used.

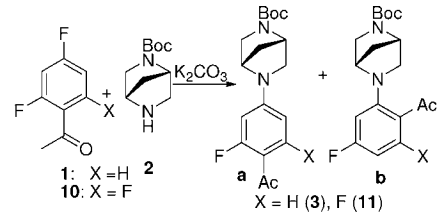
This optimal solvent for *para*-substitution, HMPA, is not environmentally friendly and requires careful handling for operator safety. While most common solvents are less hydrogen-bond basic than HMPA, ionic liquids[12,13] represented intriguing possible alternatives to the phosphoramide. For example, commercially available ethyl-3-methylimidazolium dimethyl phosphate has been reported[14a] to have comparable SHBB to HMPA and was used to replace the toxic solvent. In further studies, we ran the S_NAr reactions (Scheme 2) between a model compound *N*-Boc-piperazine (**6**) and three activated 2,4-difluoroarenes (**1**, **4**, **5**) to gain additional insight into the reaction mechanism.

Consistent with the earlier studies, 2,4-difluoroacetophenone (**1**) provided the *para*-substituted product **7a** in good correlation with the SHBBs of dioxane, acetonitrile, and HMPA. The reaction in the ionic liquid **IL1** gave a mixture of 96:4 favoring **7a** as expected. In contrast, when the ionic liquid **IL2** which has similar polarity but is much less hydrogen-bond basic than **IL1**[14b] was used, the *ortho*-product **7b**[15] was dominant. The electrophile 2,4-difluorobenzonitrile (**4**) should not be able to form a cyclic transition state due to its linear geometry (**TS-C**). The observed result, that the regioselectivity of the S_NAr for **4** differed much less dramatically in all four polar solvents regardless of their SHBB, supports our hypothesis. 2,4-Difluoronitrobenzene (**5**)[16] is expected to possess a favorable conformation[17] for the cyclic transition state, thus favoring formation of the *ortho*-isomer. Indeed, the ratio of **9a** to **9b** was always lower than that of **7a** to **7b**, as they followed the same trend across a variety of solvents. Overall, for substrates **1**, **4**, and **5**, five of the six possible regioisomers can be selectively synthesized in excellent isolated yields (76−98%)[18] under the appropriate conditions.

With the optimized solvents for either *para* or *ortho* isomer synthesis in hand, we were able to selectively prepare both regioisomers of aminofluoroacetophenone **3** and aminodifluoroacetophenone **11** (Scheme 3). In ionic liquid **IL1**, the reaction of amine **2** and polyfluoroacetophenone **1** or **10** gave predominately the *para*-isomers **3a** or **11a**, while in dioxane the reaction afforded only the *ortho*-isomer **3b** or **11b**, all in good yields.

In summary, we have demonstrated that SHBB plays an important role in controlling the regiochemistry of S_NAr reactions of activated polyfluoroarenes and secondary amines through its effect on amine hydrogen bonding in the transition state. A regioselective amination of activated polyfluoroarenes has been developed, and efforts are ongoing to expand this methodology to other substrates and nucleophiles.

Scheme 3. Regioselective Amination of Polyfluoroacetophenones[a]



ArF	solvent	temp (°C)	time (h)	prod.	**a**:**b**	yield[b] (%)
1	**IL1**	70	70	**3a**	>98:2	80
1	Dioxane	100	48	**3b**	<2:98	86
10	**IL1**	70	21	**11a**	92:8	67
10	Dioxane	100	24	**11b**	<2:98	96

[a] Reaction conditions: 1.0 equiv **2**, 1.2-2 equiv **1** or **11**, 3.0 eq K_2CO_3. [b] Isolated yield of the major isomer.

Acknowledgment. We thank Drs. T. Mansour and J. Ellingboe (Wyeth Research) for their support to this work and also thank Dr. S. Kwon (Wyeth Research) for her help in the preparation of the manuscript.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It has been known that hydrogen bond acceptor solvent can accelerate S_NAr reactions. For a recent example, see: Banjoko, O.; Babatunde, I. A. *Tetrahedron* **2005**, *61*, 8035–8040.

(12) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH Verlag: Stuttgart, Germany, 2002; pp 174−288.

(13) Recent examples on the use of ionic liquids in S_NAr reactions: (a) D'Anna, F.; Marullo, S.; Noto, R. *J. Org. Chem.* **2008**, *73*, 6224–6228. (b) Newington, I.; Perez-Arlandis, J. M.; Welton, T. *Org. Lett.* **2007**, *9*, 5247–5250. (c) D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 5144–5150.

(14) The SHBBs of **IL1** and **IL2** are reported in Kamlet−Taft parameters (β: 1.0(HMPA), 1.0(**IL1**), 0.2(**IL2**)) rather than pKHB. (a) Fukaya, Y.; Hayashi, K.; Wada, M.; Ohno, H. *Green Chem.* **2008**, *10*, 44–46. (b) Baker, S. N.; Baker, G. A.; Bright, F. V. *Green Chem.* **2002**, *4*, 165–169.

(15) A good yield of **7b** has been reported with DMF as solvent: Tucci, F. C.; Tran, J. A.; Jiang, W.; Pontillo, J.; Marinkovic, D.; White, N. S.; Arellano, M.; Fleck, B. A.; Wen, J.; Saunders, J.; Foster, A. C.; Chen, C. *Lett. Drug Des. Discovery* **2006**, *3*, 311–315.

(16) A contrary result in **IL2** has been reported: Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Tetrahedron Lett.* **2003**, *44*, 2217–2220.

(17) For 2,4-difluoroacetophenone, the O-*trans* rotamer is more stable than the O-*cis* rotamer. See: Adcock, W.; Rizvi, S. Q. A. *Aust. J. Chem.* **1973**, *26*, 2659–2663.

(18) Details in Supporting Information(Table S3).